SCIENCE

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ACIDOSIS[1]

I

FOR many years students of metabolism, of general physiology and of pathology have been investigating various aspects of the acid-base equilibrium of the body, always with an eye to the problem of acidosis, but at first with small success in unifying our knowledge of that complex subject. Successively it has been shown that in acidosis there may be a production of β-oxybutyric acid or some other specific defect of metabolism, an increase of the urinary ammonia, a diminution of the total carbonic acid of the blood, and of the blood's bicarbonate, an increase of its concentration in hydrogen ions, a diminution in the concentration of carbon dioxide in the alveolar air and of the free carbonic acid in the blood, an impairment of the affinity of the red corpuscles for oxygen, and a depletion of the alkali reserves of the body. Not all of these changes, however, are invariably present, and much confusion has resulted from the attempt to distinguish essential or primary phenomena.

At length it has become clear that acidosis is, from the standpoint of physical science, no simple and unitary state or process, but that, like metabolism or respiration, its unity is biological or functional, and that it consists in any disturbance, large enough and so long enduring as to be properly called pathological, of the regulation of alkalinity in the body. What are the disturbances to which this regulatory process is liable? They are such as are made possible by its normal and essential

[1] The Samuel D. Gross lecture, 1916.

peculiarities and general characteristics. These peculiarities can only be the object of special physiological investigations and the subject of special physiological knowledge. But in great part the more general characteristics are those of all organic regulations, and at this very point organic regulation is to-day best understood and analyzed. Accordingly, the description of acidosis must rest upon a clear definition of the nature of organization itself; it may then, in turn, help to define the larger problem.

This conclusion points straight back to Aristotle, whose great attainments as a zoologist together with his extreme virtuosity in conceiving and applying abstract ideas and formulas led him to an analysis of organization that remained the best for more than two thousand years. The words of Aristotle are as follows:

> The animal organism must be conceived after the similitude of a well-governed commonwealth. When order is once established in it there is no more need of a separate monarch to preside over each several task. The individuals each play their assigned part as it is ordered, and one thing follows another in its accustomed order. So in animals there is the same orderliness—nature taking the place of custom—and each part naturally doing his own work as nature has composed them. There is no need then of a soul in each part, but she resides in a kind of central governing place of the body, and the remaining parts live by continuity of natural structure, and play the parts Nature would have them play. [''De motu animalium,'' II., 703a, 30–35, Oxford, 1912.]

This statement surpasses the efforts of the modern philosophers, who either have not understood the problem at all, or, like Leibnitz and Kant, have but imperfectly conceived it. The earlier modern biologists are also inferior to Aristotle, for when they have perceived the riddle of organization, it has led them into sterile vitalistic theories or mere bewilderment. But during the last century there took place a steady improvement in the biological analysis and lately the subject has been partly cleared of misunderstanding, so that it is to-day in the minds of most thoughtful investigators.

In the nineteenth century the concept of *organization* appears for the first time as an explicit postulate of scientific research. Of course there has never been a period when the idea of *function* was absent from physiological investigation. And it would be an almost hopeless task to trace the transformation of this idea, with widening experience, into the larger one of organization. Provisionally it may therefore suffice to note the conscious and deliberate use of the latter idea in Cuvier's so-called law. According to this hypothesis it is possible after a careful study of any one part of an animal, for example a tooth, to reconstruct the whole. Nothing could correspond more perfectly with Aristotle's original position concerning the organic relation between the parts and the whole.

Physiology was more deliberate in setting up the principle, because organic activity is harder to define and to describe. At least as early as the time of Johannes Müller the idea was clearly grasped. But not until the establishment of experimental morphology did it become overtly a guiding principle of physiological research. One very important influence toward this result is to be found in the speculations of von Baer.

The truly Aristotelian idea of internal teleology of the organism is at the bottom of von Baer's biological philosophy. Bichat and he are the first of the *organicists*. Their successor is Claude Bernard. This great man, whose purely mechanistic researches stand at the foundation of many departments of physiology, steadily exerted all his influence in favor of the idea of organization. He recognized a directive and organizing idea in the animal, and again and again insisted upon it. Yet his analysis of the problem, like that of von Baer, was not

complete. Though he, like all other physiologists, employed the idea of functional activity as a guide in research, though he was fully aware of Cuvier's method in paleontology, his just concern for the integrity of physiological method beguiled him into declaring that "the metaphysical evolutive force by which we may characterize life is useless in science, because, existing apart from physical forces, it can exercise no influence upon them."

This, strange to say, is an old error of Kant's. It is as if one should declare that the idea of the periodic system of the elements is useless to science, because, existing apart from the physical forces, it can exercise no influence upon them. What Claude Bernard well knew, but failed here to point out, is that organization, like the second law of thermodynamics, is a condition of those physio-chemical phenomena which were the subject of his investigations. At times, however, he stated the case more correctly.

During the later years of von Baer and Claude Bernard, the ideas of Darwin were accomplishing a revolution in general biology. Not the least important result was at least temporarily to establish adaptations as the most positive of realities. Yet an adaptation is only to be defined in terms of organization. In the orthodox Darwinian view it is that which contributes to the preservation of the whole. There is nothing in its merely physical character which enables us to recognize it as an adaptation. Only its function reveals its true nature.

In the course of time some of Darwin's original positions have been weakened and the more extreme views of his followers overthrown. As a result this manner of thinking about adaptation is somewhat out of fashion. But it endured quite long enough to leave its mark upon several departments of the science. And it is very doubtful if any one will be bold enough ever again to put aside the idea of function itself or to deny its necessary implications.

Meanwhile a number of independent lines of investigation have arisen from Darwin's researches. One of the most interesting of these is the study of experimental morphology to which Sachs gave an impetus. This subject appears to have developed, partly at least, as the realization of a program of research founded upon Roux's quasi-philosophical analysis of the characteristics of life.

Such a process is a genuine curiosity in the history of science. According to Roux the living being may be defined as a natural object which possesses nine characteristic autonomous activities, *e. g.*, autonomous excretion, autonomous ingestion, autonomous multiplication, autonomous transmission of hereditary characteristics, etc. This conception, as Roux admits, is closely related to Herbert Spencer's famous conception of life as "the continuous adjustment of internal relations to external relations." Roux's discussion of the subject was independent of Spencer's influence and, in its specification of conditions, his analysis possesses certain advantages over the English philosopher's more abstract statement. But, from the standpoint of physical science, it is gravely deficient in method and has never been regarded as more than a preliminary statement of the several physiological aspects of the fact of organization.

What has given Roux's investigation a certain value and influence is that there is thus presented, however dogmatically, a provisional discrimination of organic activities as a basis for the experimental physiological study of organization itself. With the foundation of experimental morphology the problem of organization assumes its proper place in physiological research. The experimental results of the new science clearly prove that the place is secure.

This department of science has developed independently, and only in recent years can its influence upon the older science of physiology be detected. The physiologists, in their more abstract and more analytical researches have usually dealt exclusively with physical and chemical phenomena. Unlike Roux's followers, they have been concerned with those things which are organized in the living being, rather than with the organization of them. Their very method of research, which proceeds from a preliminary analysis of the factors of organization, has obscured the larger biological problem.

At length Pavlov's researches on the glands of digestion, the study of internal secretions and hormones, Sherrington's investigation of the integrative action of the nervous system, Cannon's study of the emotions, and many other independent lines of investigation have cleared the ground, and at the present moment the physico-chemical treatment of the problem of organization is widely, if somewhat vaguely, recognized as the ultimate goal of physiological research. An interesting statement of the present condition of physiology in this respect may be found in Haldane's little book "Mechanism, Life and Personality." It is doubtful, however, if all the philosophical conclusions that Haldane draws can be regarded as well founded.

In the study of metabolism, which has also had an independent development, the idea of organization has long dominated research. This is due to the fact that here the concept of equilibrium can not be avoided. At an early period in the history of the science it was discovered that a normal organism is in a state of nitrogen equilibrium. That is to say, the composition, in respect of compounds of nitrogen, is steadily preserved, through the regulation of a long chain of intricate chemical processes. Day by day the ingestion of nitrogen is approximately equal to the excretion. A modification of the diet may cause a temporary disturbance of the condition, but this is soon restored. The phenomena of growth and disease are found to involve more enduring changes. Hereupon by a process of reasoning patterned upon that of physical science, growth is declared to involve nothing more than other phenomena superimposed upon the underlying conditions, thereby modifying the observed facts in such manner that the fundamental state is partly obscured. And disease is after all, in its very essence, a disturbance of organization; in short, diseases of metabolism involve by definition disturbances of equilibria, which may or may not be compensated.

Further research reveals similar equilibria concerning carbon, sulphur, phosphorus and the other elements. The results are extended to definite chemical compounds such as water, salt, sodium bicarbonate, glucose and the like. It is perceived that the equilibria of temperature, of volume, of alkalinity, which involve physico-chemical states, are truly analogous phenomena.

Meanwhile it has always been clear that within certain limits the existence of these equilibria is essential to the preservation of life itself, and that they might have been taken for granted. The real question has been to define the normal and pathological fluctuations, their duration, their limits and their relations to other phenomena. In short, so far as these problems are concerned, the study of metabolism has consisted in an attempt to describe as thoroughly as may be, and if possible to explain, the fluctuations of the approximately constant physical and chemical conditions of the body. In other words, the task of the investigator has been to make known the facts concerning the regulation of the ultimate physical and chemical constitution of

the organism. In this undertaking he has always kept in mind the idea that the organism exists in a state of dynamic equilibrium, just as it was long ago conceived by Cuvier, and more vaguely by Hume, and by Lucretius.

Now this idea of regulation, so familiar in the investigations of the temperature of the body, and in many other general problems of metabolism, is the very concept to which all the other independent investigations of organization as a physiological problem also lead. Thus Roux has long since declared, and recently reasserted the belief, that the capacity of autonomous regulation of all nine of his elementary characteristics is quite the most important of all the peculiarities of life. For example, he thinks that this is what makes possible the direct adaptation to the environment, or, in other words, the acquiring of characteristics. In like manner the action of hormones, the integrating function of the nervous system, and the phenomena of emotional excitement investigated by Cannon are all regulatory.

It is now possible to see that Herbert Spencer's conception of life as "the continuous adjustment of internal relations to external relations," though doubtless far from satisfactory as a characterization of life itself, is really a true statement of the phenomena of organization. Vague though it may be, it is confirmed by the results of experimental morphology, of physiology and of the science of metabolism, and I suspect that pathology affords some of the most striking justifications for such a view. Indeed pathology has its prerogatives, and of these not the least is to follow up the disturbances which, step by step, result from a single lesion or deranged activity until they close a vicious circle, to note the compensatory changes, regenerations and repairs that oppose this process, and thus to perceive the organism as a whole acting so as to preserve that state of dynamic equilibrium which is essential to life itself.

But Spencer's formula is at best imperfect and needs to be modified in order to conform more exactly to Aristotle's thought. Perhaps we may say that life is to be conceived as the continuous adjustment of internal relations to the state of the organism as a whole in accordance with changes of internal and external relations. Yet I can not believe that such formulas are of much account. What we need to know and always to remember is that organization qualifies the body mechanisms. They *are* mechanisms *and also* they are organized. It is in no sense a form of vitalism that is implied in this statement, nor can I think it, as Haldane believes, antimechanism. While I am in hearty agreement with many of Haldane's positions, I can not but repudiate this view. Yet a doctrine essential to all genuine biological progress does arise from this statement, and we are all indebted to Haldane for making it clear and insisting upon it. This doctrine teaches a very necessary truth concerning our present problem of acidosis, viz., that there is no one process or phenomenon which is the fundamental or essential one, but that each is integral, at once as cause and as effect in a cycle of pathological changes whose onset may be at any one of many points and which as a whole, as a cycle, constitutes the deranged acid-base metabolism. But this, moreover, is not the whole of the matter, for, just as the parts of this cycle engage in the whole of the process of acid-base metabolism, so do they also engage, as parts, in other processes, some of them in the respiration, some in the process of excretion, and so on indefinitely. Thus the condition known as acidosis can only be truly conceived in terms of the organization of the body as a whole. Such is the abstract nature of the subject; with this the known facts correspond.

II

From its very beginning, Arrhenius's theory of ionization emphasized the peculiar importance of the ions of hydrogen and hydroxyl. As products of the electrolytic dissociation of water these ions must be present in all aqueous liquids. As products of the dissociation of acids in one case and of bases in the other, they must be essential factors, or at least the only constant factors, of acidity and alkalinity in aqueous solutions.

Methods for the estimation of the concentration of these ions were presently found, and before long successfully, if rather roughly, applied to physiological problems. Thus it was proved that the reaction of blood is nearly neutral and very constant.

Meanwhile the theory was extended, with the help of the mass law, until it became a quantitative theory of acidity, neutrality and alkalinity. The principal results of this development of the subject, so far as they concern the biologists, are as follows:

First, the product of the concentrations of hydrogen and hydroxyl ions (at constant temperature) is approximately constant.

$$(\overset{+}{\mathrm{H}}) \cdot (\overset{-}{\mathrm{O}}\mathrm{H}) = c.$$

Therefore the concentrations of these two ions always vary inversely.

$$(\overset{+}{\mathrm{H}}) = \frac{c}{(\overset{-}{\mathrm{O}}\mathrm{H})}.$$

Secondly, if for convenience, just as the histologist uses microns instead of meters, we adopt as unit concentrations of hydrogen and hydroxyl ions a very small quantity, viz., the concentration of these ions in neutral solutions, the value of this constant becomes unity.

$$(\overset{+}{\mathrm{H}}) \cdot (\overset{-}{\mathrm{O}}\mathrm{H}) = 1,$$

$$(\overset{+}{\mathrm{H}}) = \frac{1}{(\underset{-}{\mathrm{OH}})}.$$

It may be noted that, using this unit of concentration, an ordinary decinormal solution of hydrochloric acid has a concentration of hydrogen ions of nearly 1,000,000; and a decinormal solution of sodium hydroxide a corresponding concentration of hydroxyl ions. Other common dilute acid and alkaline solutions are only less remote from the concentrations of neutral solutions and of blood.

Thirdly, upon this basis the definitions of neutrality, acidity and alkalinity are as follows:

For neutrality,

$$(\overset{+}{\mathrm{H}}) = 1 = (\overset{-}{\mathrm{O}}\mathrm{H}).$$

For acidity,

$$(\overset{+}{\mathrm{H}}) > 1 > (\overset{-}{\mathrm{O}}\mathrm{H}).$$

For alkalinity,

$$(\overset{+}{\mathrm{H}}) < 1 < (\overset{-}{\mathrm{O}}\mathrm{H}).$$

Finally, in any solution containing a weak acid and its salts with one or more bases, regardless of the other components of the solution, the concentration of hydrogen ions is approximately proportional to the ratio of free acid to combined acid.

$$(\overset{+}{\mathrm{H}}) = k\frac{\mathrm{HA}}{\mathrm{BA}}.$$

This relation, however, holds only when the ratio of acid to salt is neither very large nor very small.

It is therefore evident that in the solution of any weak acid, when the quantities of free and combined acid are equal, the value of $(\overset{+}{\mathrm{H}})$ is k; if the ratio of acid to salt be 10 : 1, $(\overset{+}{\mathrm{H}})$ is 10 k, if the ratio be 1 : 10 $(\overset{+}{\mathrm{H}})$ is 0.1 k.

This is the total outcome of the theoretical analysis so far as it is necessary for a general understanding of the biological problem.

We may now turn to the special case of carbonic acid. For this substance the value of k, expressed in our present units, is about 5. Accordingly, in a solution of car-

bonic acid and bicarbonate, if the ratio of acid to salt be 10 the concentration of hydrogen ions must be 50, if the ratio be 1 the concentration will be 5, and if the ratio be 0.1 the concentration will be 0.5.

Thus we can see why carbonate solutions are almost always nearly neutral (*e. g.*, $100 > (\overset{+}{H}) > 0.01$), and, taking account of the universal distribution of free and combined carbonic acid in the ocean, in lakes and streams, and in all organisms, we understand the primary cause of the approximate neutrality of nearly all natural solutions, both organic and inorganic, upon the earth. In blood the concentration of hydrogen ions is about one third of the present unit, hence the ratio of free to combined carbonic acid must be less than 1:10.

In general it is evident that when the value of k for an acid is nearly 1 solutions containing that acid and its salts will be nearly always neutral; but that if the value of k differs largely from 1 such solutions will be nearly always appreciably acid or alkaline.

Beside carbonic acid, there is but one biologically common acid substance, viz., phosphoric acid after one hydrogen has been neutralized by base as in acid sodium phosphate, that possesses the value of k nearly equal to 1. Most weak acids have a value hundreds or thousands of times greater. Phosphate solutions are therefore commonly nearly neutral, and they share with carbonate solutions the function of preserving the constant alkalinity of the body.

It is easy roughly to demonstrate the general character of such acid-base equilibria with the help of the phosphates. Thus, for example, a solution of acid sodium phosphate has a faintly acid reaction, a solution of ordinary sodium phosphate an alkaline reaction, but almost any mixture of the two salts is neutral to ordinary indicators, and will take up strong acids or alkalis in large quantities without apparently changing its reaction. Of course every drop of acid or of alkali does change the reaction, but the change is so slight that it can not be detected by ordinary means. This depends upon the fact that strong acids and bases combine quantitatively with the alkaline or acid phosphate:

$$HCl + Na_2HPO_4 = NaCl + NaH_2PO_4,$$
$$NaOH + NaH_2PO_4 = Na_2HPO_4 + H_2O.$$

Accordingly, there is only a change in the ratio between the concentrations of the two phosphate salts, and of hydrogen ion concentration in due proportion, according to the analysis already given.

If the solution is supposed to contain bicarbonates, as well as phosphates, the above experiment fully illustrates the general character of the process by which acids are immediately neutralized in the body. The proteins, to be sure, are also involved, but their share in the process is small, though not physiologically insignificant.

Upon this physico-chemical basis the physiological processes are erected. It is as a means of restoring bicarbonate and alkaline phosphate from the products of reaction of these substances with acids, or as a means to neutralize acid, and thus prevent its reaction with bicarbonates and phosphates, that ammonia is produced in the metabolism.

In like manner the acidity of the urine is the result of the reversal in the kidney of the reaction by which acids have been neutralized in the body. In the renal function phosphates almost alone are concerned. Therefore the process may be described as follows: In the blood, as the result of the production of acid, a certain amount of alkaline phosphate has been converted into acid phosphate, so that the ratio of acid phosphate to alkaline phosphate has been

slightly increased. (Under normal circumstances this change is probably infinitesimal.) The kidney now removes relatively a still larger amount of acid than of alkaline phosphate, perhaps on account of changes in the blood bicarbonate rather than in the phosphate, and thus restores the ratio of base to acid in the blood. Here the essential factor is the ability of the kidney widely to vary the ratio of acid to alkaline phosphate without large variation of the hydrogen ion concentration of the urine. This very important fact once more depends upon the favorable value of k for acid phosphate.

It is because, in the normal individual, both the production of ammonia and the ratio of acid to alkaline phosphate in the urine are variable within wide limits, and can be made to conform exactly to the varying ingestion and production of acid in the body, that the fundamental physico-chemical apparatus can be kept intact and accurately adjusted.

A further factor in the process is the activity of the lung in excreting carbonic acid. This substance is the chief excretory product of the organism. As such it must be eliminated promptly and completely. Moreover, in that it leaves the body not in aqueous solution and as an acid, but almost exclusively in the form of gaseous carbon dioxide, there is no possibility of any variation of the permanent effect produced upon the reaction of the body by the elimination of a definite amount of it. In the final regulation by excretion it is not, therefore, concerned. And yet it has, in the process of excretion, a very important rôle in regulating the reaction of the body. This depends upon the fact that carbonic acid is not only a waste product, but also a normal constituent of the blood, and, as such, a principal factor in the physico-chemical regulation. Thus, if the ratio of carbonic acid to bicarbonates in a normal individual were 1:15, a large production of acid might cause a destruction of a third part of all the bicarbonates, producing in its place an equivalent amount of free carbonic acid. This, if nothing else occurred, would reduce the relative amount of bicarbonates from 15 to 10, and simultaneously increase the free carbonic acid from 1 to 6. The ratio would now be 6:10, and since the hydrogen ion concentration is porportional to this ratio, this ion would suffer a nearly ten-fold increase of concentration. But at this point, or, more strictly speaking, continuously during the process, the excretory function intervenes. There is a tendency for the respiratory process to hold the tension of carbonic dioxide in the blood nearly constant. This is the reason why carbonic acid has sometimes been thought the respiratory hormone. Assuming that the exact quantity of carbonic acid set free by the reaction of neutralization were thus eliminated, the ratio would be reduced to 1:10, and the hydrogen ion concentration would rise but one third above its original value. More recent investigations, however, have shown that a tendency to acidity is accompanied by a lowering of the tension of carbon dioxide. Let us suppose that in this case the tension was lowered one third. The free carbonic acid of the blood would then become 0.67 instead of 1.00, and the ratio of acid to salt 0.67:10, which is exactly equal to 1:15, the original ratio. Accordingly, the hydrogen ion concentration would be restored exactly to its original value, and the regulation by excretion would be quite perfect. Now there is abundant evidence to show that something very much like this is always occurring in the body, and, on the whole, I believe that the most delicate of all means to regulate the reaction of the body is to be found in

this variation of the tension of carbonic acid during its excretion. Such considerations have strengthened the hypothesis that the hydrogen ion is the true respiratory hormone. Originally suggested as a guess, this theory has been supported by many investigations. But I think that it marks the opening rather than the closing of a chapter in physiology, for the subject is involved in many complexities.

The whole physiological equilibrium may now be concisely summed up. The hydrogen ion concentration of the body has been seen to depend upon the ratio

$$\frac{H_2CO_3}{NaHCO_3}.$$

Acid reacting with this system causes a diminution of the denominator and an increase in the numerator of the fraction, the value of the fraction increases, and with it the hydrogen ion concentration. Hereupon the lung reduces the value of the numerator by diminishing the concentration of carbon dioxide in blood and alveolar air, the value of the fraction is restored more or less exactly to its original value and with it the concentration of the hydrogen ion. But the denominator is still below normal. To offset this, there occurs, on the one hand, a production of ammonia which takes the place in the urine of alkali existing as salt in the blood. This alkali recombines with carbonic acid, forming bicarbonate, and thus increasing the denominator. On the other hand, the kidney removes less alkali in combination with phosphates than exists in this state in the blood. This alkali, too, helps to regenerate sodium bicarbonate, and thus to increase the denominator. Both of these processes are so regulated that the denominator is restored to normal. The concentration of carbonic acid responds through the activity of the respiratory mechanism, and the organism returns to its normal state.

These processes, of course, go on simultaneously and not in succession. They are, moreover, far less simple than such an analysis admits, for on the one hand the interaction of phosphates and proteins has not been fully described, and, on the other hand, many of these variations influence other conditions and processes in the organism.

Among these effects are the influence of carbonic acid concentration and of the hydrogen ion on the affinity of hemoglobin for oxygen and on the volume of the red corpuscles. More general is a necessary, but at present indeterminate, effect on the distribution of electrolytes in the body, on the osmotic pressure, on the state of colloids, and on the volume. I fully believe that such effects are real and that when acid is produced through long periods and in large quantities in particular organs or tissues, as during diabetes, they may well surpass the direct effects of the simple chemical reactions of acid in the pathological complex, and produce a condition very different indeed from that of experimental acidosis. For in such conditions the whole physico-chemical composition of the cell, its concentrations and colloidal equilibria, might be sensibly altered.

But such guesses are one thing and the detailed and very dogmatic speculations of Dr. Martin Fischer quite another. And I feel obliged to say that there is not one particle of evidence for his conclusions, which are indeed inconsistent with, or totally without bearing upon, all the existing quantitative information that we possess upon this subject.

III

What then is acidosis? Evidently a condition lacking necessary connection with

the production of oxybutyric acid or with the magnitude of the hydrogen ion concentration in blood; still less a condition involving the existence of acid in the blood. It is often characterized by high urinary ammonia, but sometimes this quantity is low; the concentration of carbon dioxide in the alveolar air is commonly low, but one can not feel sure that this is invariably the case; in acidosis the oxygen capacity of the blood seems to be generally diminished, but we do not yet understand this subject well enough to be sure that compensatory changes may not take place. Upon the whole I think that we come nearest to certainty if we say that acidosis must involve a depletion of the body's alkali reserves, and specifically a depletion of the bicarbonate of the blood. So long as this has not taken place the pathological condition can not amount to much, so far as the acid-base equilibrium is concerned; when this defect is established the whole chain of causation, involving breathing, oxidation, nitrogen metabolism, renal activity and so on, has been set in motion.

The cause of the condition may vary widely. It may be due to the production of acid, or the ingestion of acid, or to lack of alkali in the food; it may be due to failure to eliminate acid, *e. g.*, acid phosphate, or to failure to produce and eliminate ammonia; but so far as can be seen it must always involve at least a diminution in the concentration of bicarbonate in the blood. As a practical maxim, we are therefore fully justified in saying that acidosis is a state of diminished bicarbonate in the blood.

Accordingly, it may also be said that the best means to the recognition of acidosis is proof of diminution in the bicarbonate of the blood. It is true that alveolar air, or the oxygen capacity of the blood, or the urinary ammonia, or the acidity of the urine, or the excretion of acetone bodies, may be definitive in any particular case. But a state of acidosis is certainly not always dependent on some of these variables, and may possibly be independent of all of them.

The most direct proof of diminution of the bicarbonate of the blood is afforded by an estimation of the capacity of the blood for carbon dioxide at a specified tension of the gas. This, or a related method, properly employed, will always give accurate information and need not make considerable demands upon the technical skill of the investigator.

But there is another method, consisting of a physiological test of the greatest simplicity and involving no experimental skill at all, which seems often to lead to equally trustworthy conclusions. The test depends upon an observation made by Sellards and also by Palmer and myself that in different pathological conditions and in different individuals the amount of soda administered by the mouth that is necessary to make the urine alkaline is a very variable quantity. Further extensive investigations of Dr. Palmer's have convinced me that this phenomenon depends on nothing but the retention of alkali by an organism whose store has been depleted, until the normal amount has been once more acquired. The addition of five or ten grams of soda to the food is enough to make the urine of a healthy person alkaline, and if more than that is retained, experience justifies the conclusion that a state of acidosis exists.

This test also points to a rational treatment of acidosis. For if sodium bicarbonate is administered at frequent intervals in quantities just sufficient to make the urine as alkaline as the blood, acidosis can not exist. The reaction of the urine can be followed closely enough even with litmus paper, a so-called amphoteric re-

action indicating that sufficient alkali has been provided, and if the reaction does not become more alkaline than this there seems to be no danger of injuring the kidney.

Of course this method may be inadequate to cope with the more complex problems of diabetic acidosis, and it is very doubtful if the alkali can always penetrate in sufficient quantities to the seat of acid production. There is, moreover, no reason to suppose that it can influence the cause of the condition. Indeed this is rather a matter of proper feeding than a therapeutic measure. For next to water and sodium chloride the concentration of sodium bicarbonate is the greatest in blood, and it seems not unreasonable to care for a sufficient supply of this substance as one does for a supply of water.

There is the more reason for bearing these conclusions in mind because acidosis is one of the commonest of pathological states. Indeed I think that it is probably more common than fever. Therefore one may conclude that in serious illness the test for acidosis should always be made, especially because it is often a very simple matter to repair the defect. And I think there is some reason to suppose that such action may occasionally be of the greatest importance.

But the use of alkali must always be deliberate and founded upon the urinary reaction, for too much alkali may be very harmful indeed. As employed by Martin Fischer in nephritis, experience has convinced me that it is a source of grave danger and, if possible, graver suffering to patients who can often expect from the physician little more than some relief from pain. Yet even in nephritis there is at present no reason to avoid the proper use of alkali. In fact, I have never known a kidney to be unable to excrete a small excess of it, and I think that we may therefore always undertake the administration of soda according to the rule above laid down, with the conviction that when the quantity of sodium bicarbonate in the body is below normal, no harm is to be expected from the action of sodium bicarbonate.

Finally, if I may be permitted to express as a precept my own conclusion of the bearing of all these intricate facts upon medical practise, it is as follows: The duty of the physician is to discover that the quantity of sodium bicarbonate in the blood is diminished, to restore that quantity to normal, and to hold it there. But while restoring it, he must never increase the quantity above normal. Thus founding practise upon exact knowledge, upon theory fully confirmed, and upon an understanding, however imperfect, of the organization of all the manifold processes of metabolism, he may hope sometimes to block a cycle of changes leading to final disintegration, and perhaps more often to alleviate discomfort and pain.

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SCIENTIFIC EVENTS

THE IRON INDUSTRY

Abnormal conditions prevailed in the iron industry during the first half of 1917, mainly on account of the war in Europe. At the beginning of the year, when pig iron was being made at the average rate of about 102,000 gross tons daily, the blast furnaces were operated at slightly reduced capacity, according to E. F. Burchard, of the Geological Survey. This rate dropped to less than 95,000 tons daily in February, but in March the rate rose to 105,000 tons daily, and in April and May it stood at more than 110,000 tons, compared with the maximum rate of 113,000 tons in October, 1916.

The prospective blast-furnace capacity seems not to have kept pace with the demand, however, as is indicated by the enormous in-